

Appln. No. 10/671,967

Response dated May 12, 2008

Response to Office Action of February 13, 2008

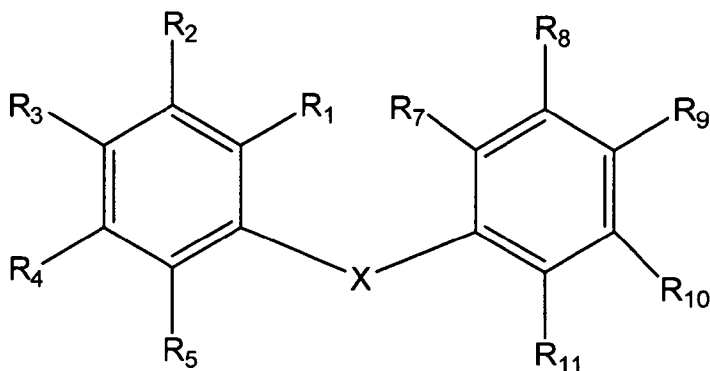
Listing of Claims:

This listing of claims will replace all prior versions and listings in the application.

1-18 (canceled).

19. (Previously Presented): A composition comprising:

a) a compound of the formula:



wherein:

X is selected from $-\text{C}(\text{O})-\text{N}(\text{R}_6)-$, $-\text{N}(\text{R}_6)-\text{C}(\text{O})-$, $-\text{CH}_2-\text{N}(\text{R}_6)-$, $-\text{N}(\text{R}_6)-\text{CH}_2-$, $-\text{N}(\text{R}_6)-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2-\text{N}(\text{R}_6)-$, $-\text{C}(\text{R}_{12})(\text{R}_{12})-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{C}(\text{R}_{12})(\text{R}_{12})-$, $-\text{C}(\text{R}_{12})(\text{R}_{12})-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2-\text{C}(\text{R}_{12})(\text{R}_{12})-$, $-\text{S}(\text{O})_2-\text{O}-$, $-\text{O}-\text{S}(\text{O})_2-$, $-\text{NR}_6-\text{C}(\text{O})-\text{Y}-$ or $\text{Y}-\text{C}(\text{O})-\text{NR}_6-$; wherein

each R_6 is independently selected from hydrogen, C_1 - C_4 straight or branched alkyl, C_2 - C_4 straight or branched alkenyl or alkynyl, Ar-substituted- C_1 - C_4 straight or branched alkyl, or Ar-substituted- C_2 - C_4 straight or branched alkenyl or alkynyl; wherein

R_6 is optionally substituted with up to 3 substituents independently selected from halo, hydroxy, nitro, cyano or amino;

each R_{12} is independently selected from R_6 , W-[C_1 - C_4 straight or branched alkyl], W-[C_2 - C_4 straight or branched alkenyl or alkynyl], Ar-substituted-[W-[C_1 - C_4 straight or branched alkyl]], Ar-substituted-[W-[C_2 - C_4 straight or branched alkenyl or alkynyl]], O-Ar, $N(R_6)$ -Ar, S-Ar, S(O)-Ar, S(O)₂-Ar, S-C(O)H, $N(R_6)$ -C(O)H, or O-C(O)H; wherein

W is O-, O-C(O)-, S-, S(O)-, S(O)₂-, S-C(O)-, $N(R_6)$ -, or $N(R_6)$ -C(O)-; and wherein

each R_{12} is optionally and independently substituted with up to 3 substituents independently selected from halo, hydroxy, nitro, cyano or amino;

Y is selected from -O-, -S-, -C/C-, -C(R_{12})₂-C(R_{12})₂-, -C(R_{12})₂- or -C(R_{12})=C(R_{12})-;

each of R_1 , R_2 , R_4 , R_5 , R_7 , R_8 , R_{10} and R_{11} is independently selected from hydrogen, halo, hydroxy, cyano, nitro, amino, -C(O)NH₂, Z-[(C_1 - C_4)-straight or branched alkyl], Z-[(C_2 - C_4)-straight or branched alkenyl or alkynyl], Ar-substituted-[(C_1 - C_4)-straight or branched alkyl], Ar-substituted-[(C_2 - C_4)-straight or branched alkenyl or alkynyl], Ar, Q-Ar, [(C_1 - C_4)-straight or branched alkyl]-Q-Ar, [(C_2 - C_4)-straight or branched alkenyl or alkynyl]-Q-Ar, O-[(C_1 - C_4)-straight or branched alkyl]-Q-Ar, O-[(C_2 - C_4)-straight or branched alkenyl or alkynyl]-Q-Ar, [(C_1 - C_4)-straight or branched alkyl]-Q- R_{13} , [(C_2 - C_4)-straight or branched alkenyl or alkynyl]-Q- R_{13} , or any two adjacent groups selected from either R_1 , R_2 , R_4 and R_5 or R_7 , R_8 , R_{10} and R_{11} may be taken together with the carbon atoms to which they are bound to form a 5 to 6-membered aromatic carbocyclic or heterocyclic ring; and

each of R_3 and R_9 is independently selected from hydrogen, halo, hydroxy, cyano, nitro, -C(O)NH₂, Z-[(C_1 - C_4)-straight or branched alkyl], Z-[(C_2 - C_4)-straight or branched alkenyl or alkynyl], Ar-substituted-[(C_1 - C_4)-straight or branched alkyl], Ar-substituted-[(C_2 -

C₄)-straight or branched alkenyl or alkynyl], Ar, Q-Ar, [(C₁-C₄)-straight or branched alkyl]-Q-Ar, [(C₂-C₄)-straight or branched alkenyl or alkynyl]-Q-Ar, O-[(C₁-C₄)-straight or branched alkyl]-Q-Ar, O-[(C₂-C₄)-straight or branched alkenyl or alkynyl]-Q-Ar, [(C₁-C₄)-straight or branched alkyl]-Q-R₁₃, [(C₂-C₄)-straight or branched alkenyl or alkynyl]-Q-R₁₃, or any two adjacent groups selected from either R₂, R₃, and R₄ or R₈, R₉, and R₁₀ may be taken together with the carbon atoms to which they are bound to form a 5 to 6-membered aromatic carbocyclic or heterocyclic ring;

wherein

Z is selected from a bond, O-, S-, S(O)₂-, C(O)-, OC(O)-, or N(H)C(O)-;

Q is selected from O, -O-C(O)-, -C(O)-O-, -N(H)-C(O)-O-, -O-N(H)-C(O)-, -N(H)-C(O)-, -C(O)-N(H)-, -O-C(O)-N(H)-, or -C(O)-N(H)-O-;

Ar is selected from phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizynyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizynyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, peridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl or phenoxazinyl or other chemically feasible monocyclic, bicyclic or tricyclic ring systems, wherein each ring consists of 5 to 7 ring atoms

and wherein each ring comprises 0 to 3 heteroatoms independently selected from N, O and S;

R_{13} is selected from [C_1 - C_{12} straight or branched alkyl] or, [C_2 - C_{12} straight or branched alkenyl or alkynyl]; wherein R_{13} is optionally substituted with 1 to 4 substituents independently selected from R_{14} or R_{15} , wherein

each R_{14} is a monocyclic or a bicyclic ring system consisting of 3 to 7 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S; wherein a CH_2 adjacent to said N, O or S may be substituted with $C(O)$; and wherein R_{14} optionally comprises up to 2 substituents independently selected from (C_1 - C_4)-straight or branched alkyl, (C_2 - C_4)-straight or branched alkenyl, 1,2-methylenedioxy, 1,2-ethylenedioxy, $(CH_2)_n-R_{16}$, $-S-(CH_2)_n-R_{16}$, $-S(O)-(CH_2)_n-R_{16}$, $-S(O)_2-(CH_2)_n-R_{16}$, $-O-(CH_2)_n-R_{16}$, or $-N(R_{18})-(CH_2)_n-R_{16}$

wherein n is 0, 1 or 2;

R_{16} is selected from halogen, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, $-OH$, $-S-(C_1-C_4)$ -alkyl, $-S(O)-(C_1-C_4)$ -alkyl, $-S(O)_2-(C_1-C_4)$ -alkyl, $-NH_2$, $-NH-(C_1-C_4)$ -alkyl, $-N((C_1-C_4)$ -alkyl) $_2$, $COOH$, $C(O)-O-(C_1-C_4)$ -alkyl or $O-(C_1-C_4)$ -alkyl; and

each R_{15} is independently selected from $-OR_{17}$, or $-N(R_{18})_2$;

R_{17} is selected from hydrogen, $-(C_1-C_6)$ -straight alkyl, $-(C_1-C_6)$ -straight alkyl-Ar, $-C(O)-(C_1-C_6)$ -straight or branched alkyl, $-C(O)$ -Ar, or $-(C_1-C_6)$ -straight alkyl-CN; and

each R_{18} is independently selected from $-(C_1-C_6)$ -straight or branched alkyl, $-(C_1-C_6)$ -straight or branched alkyl-Ar, $-(C_1-C_6)$ -straight alkyl-CN, $-(C_1-C_6)$ -straight alkyl-OH, $-(C_1-C_6)$ -straight alkyl- OR_{17} , $-C(O)-(C_1-C_6)$ -straight or branched alkyl, $-C(O)$ -Ar, $-S(O)_2-(C_1-C_6)$ -

straight or branched alkyl, or $-S(O)_2-Ar$; wherein

any alkyl, alkenyl or alkynyl group is optionally substituted with 1 to 3 independently selected halo groups; and

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally substituted with 1 to 3 substituents independently selected from halo, hydroxy, nitro, cyano, amino, (C_1-C_4) -straight or branched alkyl; $O-(C_1-C_4)$ -straight or branched alkyl, (C_2-C_4) -straight or branched alkenyl or alkynyl, or $O-(C_2-C_4)$ -straight or branched alkenyl or alkynyl;

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally benzofused; with the provisos that:

at least two of R_1 , R_2 , R_3 , R_4 , or R_5 is hydrogen;

no more than two of R_1 , R_2 , R_3 , R_4 , or R_5 comprises Ar;

at least two of R_7 , R_8 , R_9 , R_{10} or R_{11} is hydrogen; and

no more than two of R_7 , R_8 , R_9 , R_{10} or R_{11} comprises Ar; and

b) a carrier, adjuvant or vehicle, which is pharmaceutically acceptable for oral administration or administration by injection.

20. (Previously Presented): The composition according to claim 19, further comprising an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, an anti-inflammatory agent, an antifungal agent, an antibiotic, or an anti-vascular hyperproliferation compound.

21. (withdrawn): A method of treating or preventing an IMPDH-mediated disease or condition in a mammal comprising the step of administering to said mammal a

composition according to claim 19 or 20.

22. (withdrawn): The method according to claim 21, wherein said IMPDH-mediated disease or condition is selected from transplant rejection, graft versus host disease, or an autoimmune disease.

23. (withdrawn): The method according to claim 22, wherein said mammal is administered an additional immunosuppressant in a separate dosage form or as part of said composition.

24. (withdrawn): A method for inhibiting replication of a virus in a mammal comprising the step of administering to said mammal a composition according to claim 19 or 20.

25. (withdrawn): The method according to claim 24, wherein said virus is selected from orthomyxovirus, paramyxovirus, herpesvirus, retrovirus, flavivirus, pestivirus, hepatotropic virus, bunyavirus, Hantaan virus, Caraparu virus, human papilloma virus, encephalitis virus, arena virus, reovirus, vesicular stomatitis virus, rhinovirus, enterovirus, Lassa fever virus, togavirus, poxvirus, adenovirus, rubiola, or rubella.

26. (withdrawn): The method according to claim 25, wherein said mammal is administered an additional anti-viral agent in a separate dosage form or as part of said composition.

27. (withdrawn): A method for inhibiting vascular cellular hyperproliferation

in a mammal comprising the step of administering to said mammal a composition according to claim 19 or 20.

28. (withdrawn): The method according to claim 27, wherein said method is useful in treating or preventing restenosis, stenosis, arteriosclerosis or other hyperproliferative vascular disease.

29. (withdrawn): The method according to claim 28, wherein said mammal is administered an additional anti-vascular hyperproliferative agent in a separate dosage form or as part of said composition.

30. (withdrawn): A method for inhibiting tumors and cancer in a mammal comprising the step of administering to said mammal a composition according to claim 19 or 20.

31. (withdrawn): The method according to claim 30, wherein said medicament is useful to treat or prevent lymphoma, leukemia and other forms of cancer.

32. (withdrawn): The method according to claim 31, wherein said mammal is administered an additional anti-tumor or anti-cancer agent in a separate dosage form or as part of said composition.

33. (withdrawn): A method for inhibiting inflammation or an inflammatory disease in a mammal comprising the step of administering to said mammal a composition according to claim 19 or 20.

34. (withdrawn): The method according to claim 33, wherein said method is useful for treating or preventing osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma or adult respiratory distress syndrome.

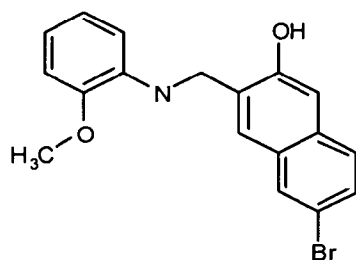
35. (withdrawn): The method according to claim 33, wherein said mammal is administered an additional anti-inflammatory agent in a separate dosage form or as part of said composition.

36. (previously presented): The composition of claim 19 or 20, wherein X is -N(R₆)-C(O)-Y-.

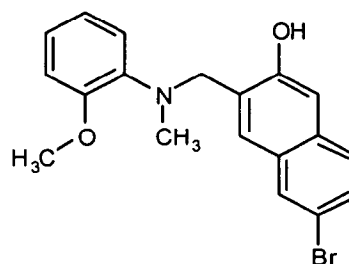
37. (withdrawn): The composition of claim 36, wherein Y is -C(R₁₂)=C(R₁₂)-.

38. (withdrawn): The composition of claim 19 or 20, wherein Q is -N(H)-C(O)-O-.

39. (withdrawn): A compound selected from the group consisting of 115 and 151;



115

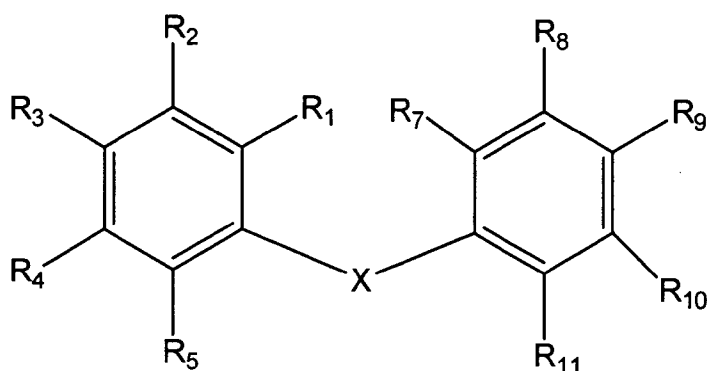


151.

40. (withdrawn): A compound selected from the group consisting of 101, 103, 104, 105, 106, 107, 110, 111, 112, 113, 114, 116, 117, 118, 119, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 148, 149, 153, 154, 155, 156, 159, 160, 162, 163, 164, 165, 166, 168, 169, 172, 173, 175, 177, 178, 179, 181, 182, 183, 184, 185, 188, 191, 192, 193 and 304.

41. (Previously Presented): A composition comprising:

a) a compound of the formula:



wherein:

X is selected from $-\text{C}(\text{O})-\text{N}(\text{R}_6)-$, $-\text{N}(\text{R}_6)-\text{C}(\text{O})-$, $-\text{CH}_2-\text{N}(\text{R}_6)-$, $-\text{N}(\text{R}_6)-\text{CH}_2-$, $-\text{N}(\text{R}_6)-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2-\text{N}(\text{R}_6)-$, $-\text{C}(\text{R}_{12})(\text{R}_{12})-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{C}(\text{R}_{12})(\text{R}_{12})-$, $-\text{C}(\text{R}_{12})(\text{R}_{12})-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2-\text{C}(\text{R}_{12})(\text{R}_{12})-$, $-\text{S}(\text{O})_2-\text{O}-$, $-\text{O}-\text{S}(\text{O})_2-$, $-\text{NR}_6-\text{C}(\text{O})-\text{Y}-$ or $\text{Y}-\text{C}(\text{O})-\text{NR}_6-$; wherein

each R_6 is independently selected from hydrogen, C_1 - C_4 straight or branched alkyl, C_2 - C_4 straight or branched alkenyl or alkynyl, Ar-substituted- C_1 - C_4 straight or branched alkyl, or Ar-substituted- C_2 - C_4 straight or branched alkenyl or alkynyl; wherein

R_6 is optionally substituted with up to 3 substituents independently selected from halo, hydroxy, nitro, cyano or amino;

each R_{12} is independently selected from R_6 , W-[C_1 - C_4 straight or branched alkyl], W-[C_2 - C_4 straight or branched alkenyl or alkynyl], Ar-substituted-[W-[C_1 - C_4 straight or branched alkyl]], Ar-substituted-[W-[C_2 - C_4 straight or branched alkenyl or alkynyl]], O-Ar, N(R_6)-Ar, S-Ar, S(O)-Ar, S(O)₂-Ar, S-C(O)H, N(R_6)-C(O)H, or O-C(O)H; wherein

W is O-, O-C(O)-, S-, S(O)-, S(O)₂-, S-C(O)-, N(R_6)-, or N(R_6)-C(O)-; and wherein

each R_{12} is optionally and independently substituted with up to 3 substituents independently selected from halo, hydroxy, nitro, cyano or amino;

Y is selected from -O-, -S-, -C/C-, -C(R_{12})₂-C(R_{12})₂-, -C(R_{12})₂- or -C(R_{12})=C(R_{12})-

each of R_1 , R_2 , R_4 , R_5 , R_7 , R_8 , R_{10} and R_{11} is independently selected from hydrogen, halo, hydroxy, cyano, nitro, amino, -C(O)NH₂, Z-[(C_1 - C_4)-straight or branched alkyl], Z-[(C_2 - C_4)-straight or branched alkenyl or alkynyl], Ar-substituted-[(C_1 - C_4)-straight or branched alkyl], Ar-substituted-[(C_2 - C_4)-straight or branched alkenyl or alkynyl], Ar, Q-Ar, [(C_1 - C_4)-straight or branched alkyl]-Q-Ar, [(C_2 - C_4)-straight or branched alkenyl or alkynyl]-Q-Ar, O-[(C_1 - C_4)-straight or branched alkyl]-Q-Ar, O-[(C_2 - C_4)-straight or branched alkenyl or alkynyl]-Q-Ar, [(C_1 - C_4)-straight or branched alkyl]-Q- R_{13} , [(C_2 - C_4)-straight or branched alkenyl or alkynyl]-Q- R_{13} , or any two adjacent groups selected from either R_1 , R_2 , R_4 and R_5 or R_7 , R_8 , R_{10} and R_{11} may be taken together with the carbon atoms to which they are bound to form a 5 to 6-membered aromatic carbocyclic or heterocyclic ring;

R_3 is selected from hydrogen, Ar, cyano, O-(C_1 - C_4)-straight or branched alkyl, O-Ar, S-(C_1 - C_4)-straight or branched alkyl, CF₃, or OCF₃;

R_9 is selected from hydrogen, (C_1 - C_4)-straight or branched alkyl, O-(C_1 - C_4)-straight or

branched alkyl, or R₉ is taken together with R₁₀ and the carbon atoms to which they are bound to form a fused benzene ring;

wherein

Z is selected from a bond, O-, S-, S(O)₂-, C(O)-, OC(O)-, or N(H)C(O)-;

Q is selected from O, -O-C(O)-, -C(O)-O-, -N(H)-C(O)-O-, -O-N(H)-C(O)-, -N(H)-C(O)-, -C(O)-N(H)-, -O-C(O)-N(H)-, or -C(O)-N(H)-O-;

Ar is selected from phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizynyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizynyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, peridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl or phenoxazinyl or other chemically feasible monocyclic, bicyclic or tricyclic ring systems, wherein each ring consists of 5 to 7 ring atoms and wherein each ring comprises 0 to 3 heteroatoms independently selected from N, O and S;

R₁₃ is selected from [C₁-C₁₂ straight or branched alkyl] or, [C₂-C₁₂ straight or branched alkenyl or alkynyl]; wherein R₁₃ is optionally substituted with 1 to 4 substituents independently selected from R₁₄ or R₁₅, wherein

each R₁₄ is a monocyclic or a bicyclic ring system consisting of 3 to 7 members per

ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S; wherein a CH₂ adjacent to said N, O or S may be substituted with C(O); and wherein R₁₄ optionally comprises up to 2 substituents independently selected from (C₁-C₄)-straight or branched alkyl, (C₂-C₄)-straight or branched alkenyl, 1,2-methylenedioxy, 1,2-ethylenedioxy, (CH₂)_n-R₁₆, -S-(CH₂)_n-R₁₆, -S(O)-(CH₂)_n-R₁₆, -S(O)₂-(CH₂)_n-R₁₆, -O-(CH₂)_n-R₁₆, or -N(R₁₈)-(CH₂)_n-R₁₆

wherein n is 0, 1 or 2;

R₁₆ is selected from halogen, -CN, -NO₂, -CF₃, -OCF₃, -OH, -S-(C₁-C₄)-alkyl, -S(O)-(C₁-C₄)-alkyl, -S(O)₂-(C₁-C₄)-alkyl, -NH₂, -NH-(C₁-C₄)-alkyl, -N((C₁-C₄)-alkyl)₂, COOH, C(O)-O-(C₁-C₄)-alkyl or O-(C₁-C₄)-alkyl; and

each R₁₅ is independently selected from -OR₁₇, or -N(R₁₈)₂;

R₁₇ is selected from hydrogen, -(C₁-C₆)-straight alkyl, -(C₁-C₆)-straight alkyl-Ar, -C(O)-(C₁-C₆)-straight or branched alkyl, -C(O)-Ar, or -(C₁-C₆)-straight alkyl-CN; and

each R₁₈ is independently selected from -(C₁-C₆)-straight or branched alkyl, -(C₁-C₆)-straight or branched alkyl-Ar, -(C₁-C₆)-straight alkyl-CN, -(C₁-C₆)-straight alkyl-OH, -(C₁-C₆)-straight alkyl-OR₁₇, -C(O)-(C₁-C₆)-straight or branched alkyl, -C(O)-Ar, -S(O)₂-(C₁-C₆)-straight or branched alkyl, or -S(O)₂-Ar; wherein

any alkyl, alkenyl or alkynyl group is optionally substituted with 1 to 3 independently selected halo groups; and

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally substituted with 1 to 3 substituents independently selected from halo, hydroxy, nitro, cyano, amino, (C₁-C₄)-

straight or branched alkyl; O-(C₁-C₄)-straight or branched alkyl, (C₂-C₄)-straight or branched alkenyl or alkynyl, or O-(C₂-C₄)-straight or branched alkenyl or alkynyl;

any Ar, aromatic carbocyclic ring or heterocyclic ring is optionally benzofused; with the provisos that:

at least two of R₁, R₂, R₃, R₄, or R₅ is hydrogen;

no more than two of R₁, R₂, R₃, R₄, or R₅ comprises Ar;

at least two of R₇, R₈, R₉, R₁₀ or R₁₁ is hydrogen; and

no more than two of R₇, R₈, R₁₀ or R₁₁ comprises Ar; and

b) a carrier, adjuvant or vehicle, which is pharmaceutically acceptable for oral administration or administration by injection.

42. (Previously Presented): The composition according to claim 41, further comprising an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, an anti-inflammatory agent, an antifungal agent, an antibiotic, or an anti-vascular hyperproliferation compound.